

B₄ 26. (Amended) The electrochemical test strip according to claim 1, wherein said strip is present in an automated instrument designed to work with test strips.

27. (Amended) The method according to claim 16, wherein said detecting and measuring steps are performed by an automated instrument designed to work with test strips.

REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-20 and 26-27 are pending after entry of the amendments set forth herein.

Claims 1-20 and 26-27 were examined and were rejected. No claims were allowed.

Please replace the paragraph beginning on page 10, line 19 with the clean version provided above. This paragraph has been rewritten to provide the application number, and patent number, for the application referenced in the paragraph. The Applicants affirm that no new matter is added to the specification by this amendment.

Please replace claims 1, 6, 12, 16, and 27 with the clean version provided above.

Claims 1, 6, 12, 16, and 27 have been amended. Claims 1, 6, 12, and 16 have been amended to replace the phrase "first and second" electrodes with the phrase "working and reference". Claim 16 has been further amended such that the claim now recites the following: (c) measuring said detected electrical signal to thereby determine the concentration of said analyte in said sample. Support for this amendment is found throughout the specification, particularly at: page 10, lines 19-24. Claims 26 and 27 have been amended to recite that the automated instrument is designed to work with test strips. Support for this amendment is found throughout the specification, and in particular at: page 10, line 24 through page 11, line 3. Claim 27 has been further amended to make the claim language consistent with claim 16, on which it depends.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

Objection to Specification

The specification has been objected to for not providing the serial number for the application referenced on pages 10-11 of the application.

This objection is rendered moot by the Applicants' amendment to the specification to insert the serial number and patent number of the application incorporated by reference. Applicants affirm that this amendment adds no new matter to the application.

Rejection under 35 U.S.C. §112, first paragraph

Claims 26 and 27 have been rejected under 35 U.S.C. §112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office states that, while the specification is enabling for a test strip and a method for determining concentration of an analyte, the specification does not enable one skilled in the art to which it pertains or with which it is most nearly connected to make or use the invention as claimed. The Office Action then analyzes the breadth of the claims, the nature of the invention, the existence of working examples, and the quantity of experimentation required.

This rejection appears to stem from a broad interpretation of the term "automated instrument" and from the Office being unable to examine the disclosure of the pending

application incorporated by reference into the instant specification, which incorporated application provides a representative instrument. As noted above, the Applicants have provided the application and patent numbers of the incorporated application. Moreover, the Applicants have amended claims 26 and 27 to recite that the automated instrument is designed to work with test strips.

Accordingly, the Applicants submit that claims 26 and 27 are fully enabled by the specification such that one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. As such, this rejection of claims 26 and 27 under 35 U.S.C. §112, first paragraph, should be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-20, 26 and 27 have been rejected under 35 U.S.C. §112, second paragraph, as assertedly indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. Each of the specific rejections is addressed individually below.

a) Claims 1-5 and 26 are asserted to be indefinite because the phrase "first and second" lacks antecedent basis. The Applicants have addressed this rejection by replacing reference to "first and second" with "working and reference", as suggested by the Examiner. Thus, Claims 1-5 and 26 are not indefinite.

b) Claims 6-11 are asserted to be indefinite because the phrase "first and second" lacks antecedent basis. The Applicants have addressed this rejection by replacing reference to "first and second" with "working and reference", as suggested by the Examiner. Thus, Claims 6-11 are not indefinite.

c) Claims 12-15 are asserted to be indefinite because the phrase "first and second" lacks antecedent basis. The Applicants have addressed this rejection by replacing reference to "first

and second" with "working and reference", as suggested by the Examiner. Thus, Claims 12-15 are not indefinite.

d) Claims 16-20 and 27 are asserted to be indefinite because the phrase "first and second" lacks antecedent basis. The Applicants have addressed this rejection by replacing reference to "first and second" with "working and reference", as suggested by the Examiner. Thus, Claims 16-20 and 27 are not indefinite.

e) Claims 16-20 and 27 are asserted to be indefinite for not reciting method steps for determining concentration and for using the term "relating". The Applicants have amended claim 16 such that the claim now recites the following: (c) measuring said detected electrical signal to thereby determine the concentration of said analyte in said sample. Thus, the claim now recites a method step for determining concentration and no longer recites the term "relating." Thus, Claims 16-20 and 27 are not indefinite.

f) Claim 26 is asserted to be indefinite because it is unclear how the recitation limits the structural components of the test strip of claim 1. The Applicants submit that one of skill in the art would understand how a test strip and an automated instrument would be adapted to function together. Thus, claim 26 is not indefinite.

g) Claim 27 is asserted to be indefinite for the phrase "employing an automated instrument." The Office asserts that it is unclear what functions the instrument performs and it is unclear at what method steps the instrument the instrument is employed. Claim 27 now specifies that the detecting and measuring steps are performed by an automated instrument designed to work with test strips. Thus, claim 27 is not indefinite.

The Applicants have addressed each of the specific rejections above. Accordingly, this rejection of Claims 1-20, 26 and 27 under 35 U.S.C. §112, second paragraph, should be withdrawn.

Rejection under 35 U.S.C. §103

Claims 1-14, 16-20, 26, and 27 have been rejected under 35 U.S.C. §103(a) as being unpatentable over McAleer et al. in view of Mizutani et al. and Backhaus et al. The Office asserts that it would have been obvious to the skilled artisan to apply the sulfonate group of Backhaus et al. to the surface modification of Mizutani et al. to thereby increase the hydrophilic properties of the surface for the expected benefit of increasing interaction with an aqueous sample.

In response and for the following reasons, the Applicants submit that one of skill in the art would not have been motivated to combine and modify reference teachings to arrive at the present invention. Moreover, any attempt to create the present invention from the cited references would not have been made with a reasonable expectation of success.

McAleer et al. simply describes a test strip, where the working electrode has a filler which has both hydrophobic and hydrophilic surface regions. Preferred fillers are non-conductive silica fillers (Col. 2, lines 39-57). McAleer makes no mention of an electrode having a surface modified with a homogenous surface modification layer made up of self assembling molecules having a first sulfhydryl end group and a second sulfonate end group, where the sulfhydryl and sulfonate end groups are separated by a lower alkyl linker group. Moreover, the test strip of McAleer does not have opposing electrodes (Fig. 1A).

Mizutani et al. describe preparation of an amperometric glucose-sensing electrode by immobilizing glucose oxidase on a polyion complex membrane (abstract). The electrode has a monolayer of 3-mercaptopropionic acid (MPA), which functions to allow passage of analyte, but prevents interferents from reaching the electrode surface (page 173). However, the MPA layer also serves as a base layer to ionically bind to the electrode a scaffold of positively charged poly-L-lysine, negatively charged poly(4-styrenesulfonate), and positively charged poly-L-lysine (polyion complex layer) (Page 175, Fig. 1). The detection system described by Mizutani et al. does not use a redox reagent system comprising at least one enzyme and a mediator. Rather, the

system described by Mizutani et al. directly oxidizes hydrogen peroxide. Hydrogen peroxide is not a redox mediator as described in the present invention, as are ferricyanide and other listed in the specification on page 9, lines 4-13.

Backhaus et al. simply state that a hydrophilic surface coating can be used to assist with the spreading of sample liquid on a substrate. According to Backhaus et al., alkyl chains with terminal thiol groups are suitable for coating gold surfaces because the thiol group binds well to gold surfaces. Backhaus et al. also states that alkyl chains with sulfonic acid groups provide a hydrophilic coating (Col 7, lines 45-49). The detection system used by Backhaus et al. does not comprise an electrochemical test strip, nor a redox reagent system, but rather is based on detection of radiation emitted from a sample.

The combination of the three references described above would not lead one of skill in the art to arrive at the instant invention because the skilled artisan would not be motivated to combine McAleer et al, Mizutani et al., and Backhaus et al. In the instant invention, the surface modification layer serves to provide a hydrophilic surface to the electrode and to prevent undesirable interfering substances, such as dust, red blood cells, etc., from reaching the surface of the electrode and reducing the performance of the test strip. However, components of the redox reagent system (e.g., enzyme and mediator) are still able to interact with the electrode and oxidize the analyte. Thus, the surface modification layer in the instant invention is provided to prevent unwanted substances from binding to the electrode.

In Mizutani et al., however, binding of additional substances to the electrode is exactly what is desired. The MPA coating described in the reference is chosen so that the polyion complex layer will ionically bind to the electrode. This is opposite to the desired purpose of the surface modification layer of the instant invention. The Office asserts that it would be obvious to modify the electrode of McAleer et al. with the MPA coating of Mizutani et al. However, the skilled artisan would not be motivated to combine McAleer et al. and Mizutani et al. because the surface coatings described in the two references serve different functions.

The Office then asserts that it would obvious to replace the carboxylate group of Mizutani et al. with the sulfonate group of Backhaus et al. because the " -2 charge of sulfonate would possess increased hydrophilic properties." However, as described above, in Mizutani et al. the negatively charged MPA coating is used to bind positively charged poly-L-lysine to the electrode, where the positive charge results from the amine in the side chain of the amino acid. Thus, the carboxylate group of MPA interacts with the amine of lysine to provide the desired interaction. While it is true that because of relatively higher ionization of the sulfonate moiety, with respect to carboxylate, the sulfonate moiety possesses increased hydrophilic properties, the sulfonate moiety also reduces interaction, such as ionic interaction, with positively charged amine groups in the terminal and side chains of the amino acid. As such, the skilled artisan, would not be motivated to substitute a sulfonate group for the carboxylate group of Mizutani et al. because it is known that ionic bonds between sulfonate groups and amines often will not form. Thus, the skilled artisan would not combine the teachings of McAleer et al. Mizutani et al. and Backhaus et al. **because the skilled artisan would not in fact substitute the sulfonate moiety for the carboxylate moiety despite the increased hydrophilicity provided by the sulfonate moiety.**

However, even if the skilled artisan were to combine the references, the skilled artisan would not have reasonably predicted that an electrode coated with the surface modification layer of the instant invention would exhibit a low contact angle measurement, fast wicking time, and storage stability for extended periods of time at elevated temperatures (page 5, lines 27 through page 6, line 2). This result was wholly unexpected to the skilled artisan based on the knowledge in the art that typical coatings exhibited higher contact angles and were subject to thermal degradations. Although Mizutani et al. states that "the electrode/polyion complex layer/GOx layer structure was a suitable way for realization of an amperometric glucose-sensing electrode with high performance characteristics," the detection system described by Mizutani et al. is not the same as the redox reagent system of the instant invention.

Finally, contrary to the assertion in the Office Action, McAleer et al. does not describe an electrochemical test strip having opposing working and reference electrodes separated by a

spacer layer as in the instant invention because McAleer discloses a coplanar or side-by-side configuration. Thus, the combination of the three cited references fails to teach or suggest all the limitations of the claimed invention.

For the reasons stated above, the skilled artisan would not be motivated to combine McAleer et al, Mizutani et al., and Backhaus et al. to arrive at the instant invention. Moreover, even if the skilled artisan were to combine the cited references, any combination of the references would not be made with a reasonable expectation of successfully arriving at the instant invention. Furthermore, the combination of the cited references fails to teach or suggest all the limitations of the claimed invention. Accordingly, this rejection of Claims 1-14, 16-20, 26, and 27 under 35 U.S.C. §103(a) should be withdrawn.

Claim 15 has been rejected under 35 U.S.C. §103(a) as being unpatentable over McAleer et al. in view of Mizutani et al., Backhaus et al., and Pritchard et al. The Office asserts that it would have been obvious to one skilled in the art to apply the palladium electrode of Pritchard et al. to the electrodes of McAleer et al. and Mizutani et al.

The deficiencies of McAleer et al., Mizutani et al., and Backhaus et al. are described above. Pritchard et al. does nothing to remedy the deficiencies of the previously cited references. First, the test strip of Pritchard et al. does not have opposing electrodes because Pritchard discloses a side-by-side or coplanar configuration. Second, Pritchard et al. simply states that palladium can be used to make an electrode of an electrochemical test strip.

Thus, Pritchard et al. provides no motivation to the skilled artisan to combine the cited references, nor a reasonable expectation of arriving at the instant invention if the references were combined, as discussed above for the rejection of Claims 1-14, 16-20, 26, and 27. Finally, Pritchard et al. fails to provide a test strip having opposing electrodes. Accordingly, this rejection of claim 15 under 35 U.S.C. §103(a) should be withdrawn.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number LIFE004.

Respectfully submitted,
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Date: 5.20.02

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VERSION WITH MARKINGS TO SHOW CHANGES MADE**IN THE SPECIFICATION**

The paragraph beginning on page 10, line 19 has been amended as follows:

Following detection of the electrochemical signal generated in the reaction zone as described above, the amount of the analyte present in the sample introduced into the reaction zone is then determined by relating the electrochemical signal to the amount of analyte in the sample. In making this derivation, the measured electrochemical signal is typically compared to the signal generated from a series of previously obtained control or standard values, and determined from this comparison. In many embodiments, the electrochemical signal measurement steps and analyte concentration derivation steps, as described above, are performed automatically by a devices designed to work with the test strip to produce a value of analyte concentration in a sample applied to the test strip. A representative reading device for automatically practicing these steps, such that user need only apply sample to the reaction zone and then read the final analyte concentration result from the device, is further described in copending U.S. application serial no. [_____] 09/333,793, now U.S. Patent No. 6,193,873 B1, entitled "Sample Detection to Initiate Timing of an Electrochemical Assay," (Attorney Docket No. LFS-77), the disclosure of which is herein incorporated by reference.

IN THE CLAIMS

Claims 1, 6, 12, 16, 26 and 27 have been amended.

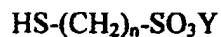
1. (Amended) An electrochemical test strip comprising:

(a) a reaction zone defined by opposing working and reference electrodes separated by a spacer layer, wherein at least one of said [first and second] working and reference electrodes has a surface modified with a homogenous surface modification layer made up of self assembling molecules having a first sulfhydryl end group and a second sulfonate end group, wherein said sulfhydryl and sulfonate end groups are separated by a lower alkyl linker group; and

(b) a redox reagent system present in said reaction zone, wherein said redox reagent system comprises at least one enzyme and a mediator.

6. (Amended) An electrochemical test strip comprising:

(a) a reaction zone defined by opposing working and reference electrodes comprising a metal surface separated by a thin spacer layer, wherein at least one of said [first and second metallic] working and reference electrodes has a surface modified with a homogenous surface modification layer made up of self assembling molecules of the formula:



wherein:

n is an integer from 1 to 6; and

Y is H or a cation; and

(b) a redox reagent system present in said reaction zone, wherein said redox reagent system comprises enzymes and a mediator.

12. (Amended) An electrochemical test strip for use in detecting the concentration of glucose in a physiological sample, said test strip comprising:

(a) a reaction zone defined by opposing working and reference electrodes comprising a metal surface selected from the group consisting of gold and palladium separated by a thin spacer layer, wherein at least one of said [first and second metallic] working and reference electrodes has a surface modified with a homogenous surface modification layer made up of 2-mercaptoethane sulfonic acid or a salt thereof; and

(b) a redox reagent system present in said reaction zone, wherein said redox reagent system comprises a glucose oxidizing enzyme and a mediator.

16. (Amended) A method of determining the concentration of an analyte in a physiological sample, said method comprising:

- (a) applying said physiological sample to an electrochemical test strip comprising:
 - (i) a reaction zone defined by opposing working and reference metallic electrodes separated by a spacer layer, wherein at least one of said [first and second] metallic working and reference electrodes has a surface modified with a homogenous surface modification layer made up of self assembling molecules having a first sulfhydryl end group and a second sulfonate end group, wherein said sulfhydryl and sulfonate end groups are separated by a lower alkyl linker group; and
 - (ii) a redox reagent system present in said reaction zone, wherein said redox reagent system comprises at least one enzyme and a mediator;
 - (b) detecting an electrical signal in said reaction zone using said metallic electrodes;
- and
- (c) [relating] measuring said detected electrical signal to [the amount] thereby determine the concentration of said analyte in said sample.

26. (Amended) The electrochemical test strip according to claim 1, wherein said strip is present in an automated instrument designed to work with test strips.

27. (Amended) The method according to claim 16, wherein said [method comprises employing] detecting and measuring steps are performed by an automated instrument designed to work with test strips.